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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 4,621,077 — 06/618,578

Issued: November 4, 1986 F 9209 11/15/95

To: Sergio Rosini and Giorgio Staibano

Assignee: Istituto Gentili S.p.A.

For: PHARMACOLOGICALLY ACTIVE BIPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS THEREFROM

Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

RESPONSE TO ORDER TO SHOW CAUSE

This is in response to the order to show cause dated January 11, 1995 [sic 1996] (the "Order") which has a nonextendible response date of two months, i.e., March 11, 1996. Applicant's response is to the Order as discussed and clarified at the interview of February 8, 1996, at the United States Patent and Trademark Office ("PTO").

Applicant through the undersigned attorney wishes to thank Ms. Karen Tyson and Mr. Hiram Bernstein of the PTO for the helpful interview held February 8, 1996. At the interview Applicant described the background and nature of the invention which resulted in the approved product FOSAMAX®, the use of which is claimed in U.S. Patent 4,621,077. Applicant requested clarification of the Order, and the PTO advised that it had two questions which are posed in the Interview Summary Record: 1) Is a salt trihydrate a salt as used in the statute, and as a commonly accepted meaning, and 2) Is the active ingredient in the tablet? It is Applicant's understanding that, as reflected in the Interview Summary Record, Agreement was reached that Applicant's response to these two questions would be a full and complete response to the Order.

In regard to the first question Applicant affirms that a salt trihydrate is a salt. Although the PTO advised that a statement on the record as to a salt trihydrate is a salt would be sufficient, Applicant provides the following in support.

The "trihydrate" designation of alendronate monosodium salt trihydrate indicates there are three molecules of water of crystallization present. The water of crystallization does not affect the fact that the compound is a salt. See for example references 1 and 2 below.

1. Page 692 from *Dorland's Illustrated Medical Dictionary* 24th edition, provides a definition of the term hydrate as "any salt or other compound that contains water of crystallization."

2. Page 214 from *Chemical Principles* 2nd edition, by M. B. Hill which indicates that copper sulfate pentahydrate is a salt.

There are many examples of drugs which are salts in the form of salt hydrates. Examples include

- DURAMORPH®: 7, 8 didehydro-4, 5-epoxy-17-methyl-(5α, 6α)-morphinan-3, 6-diol sulfate (2:1) (salt) pentahydrate.

- LOMOTIL®: one ingredient is atropine sulfate, which is endo(±)-α-(hydroxymethyl) benzeneacetic acid 8-methyl-8-azabicyclo [3.2.1] oct-3-yl ester sulfate (2:1) (salt) monohydrate.

Applicant has not conducted a complete search of patents receiving patent term extension, however, patent term extension has been granted for U.S. Patent 4,695, 578 wherein the product is ZOFRAN®, chemically 1,2,3,9-Tetrahydro-9-methyl-3[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate. Thus, salt hydrates (in this case, a hydrochloride dihydrate) have been approved for patent term restoration.

In summary the dictionary definition supports the accepted meaning that salt hydrates are salts; the chemistry text provides a particular example of a salt hydrate referred to as a salt, and salt hydrates have been approved for patent term extension as shown in the "578" patent.

In respect to the second question Applicant herein affirms that the active ingredient of FOSAMAX®, i.e., alendronate monosodium salt trihydrate is present in the tablet. Although the PTO advised that this statement on the record would be sufficient, Applicant submits a copy of the FOSAMAX® product circular, which on the first page states that tablets of FOSAMAX® contain alendronate monosodium salt trihydrate.

Applicant submits that the above is fully responsive to the Order as clarified at the February 8, 1996 interview and that U.S. Patent 4,621,077 claims a method of using the approved product FOSAMAX®, as defined in 35 USC § 156. Applicant, as stated in its application for extension of patent term, maintains that U.S. Patent 4,621,077 satisfies all the eligibility requirements for patent term restoration under 35 USC § 156(a).

Applicant submits that it has fully complied with the PTO's request and trusts that the above comments allow the PTO to conclude that U.S. Patent 4,621,077 is eligible for extension of patent term under 35 USC § 156 and facilitate the grant of patent term restoration.

If the above comments are not deemed sufficient, Applicant reserves the right to submit additional arguments and evidence. Applicant requests that if the PTO requires any additional information or response in regard to any point raised in the Order, or at the interview, that the undersigned attorney promptly be contacted at the number noted below.

Respectfully submitted,

By _____

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Date: February 14, 1996

Attachments:
(1) Page 692 from *Dorland's Illustrated Medical Dictionary* 24th Edition.
(2) Page 214 from *Chemical Principles* 2nd Edition
(3) Fosamax® Product Circular
(4) *Physicians' Desk Reference* 49th Edition 1995 pages 975, 2327

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